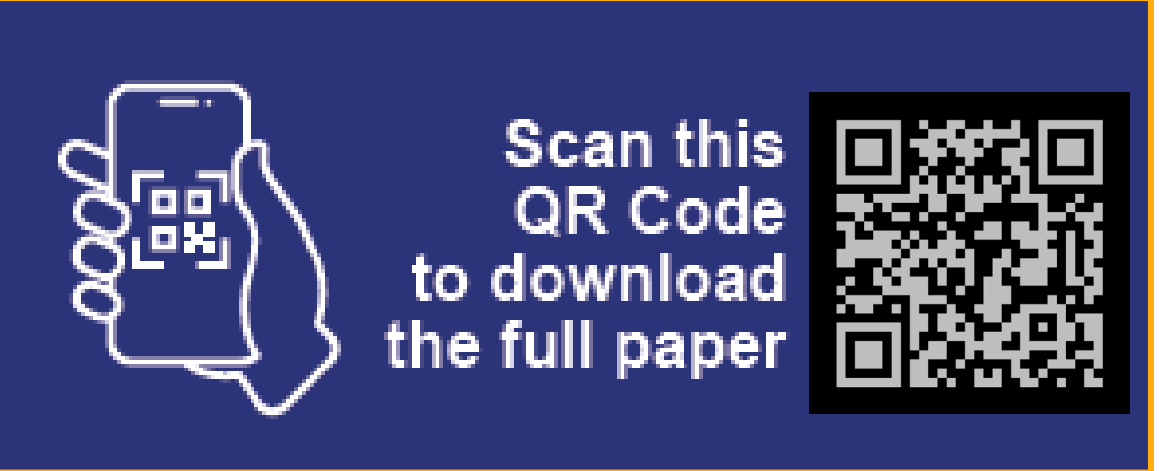# Population Pharmacokinetic (PopPK) Model of AB521 (Casdatifan), a Small Molecule Inhibitor of HIF-2α, in Healthy Participants

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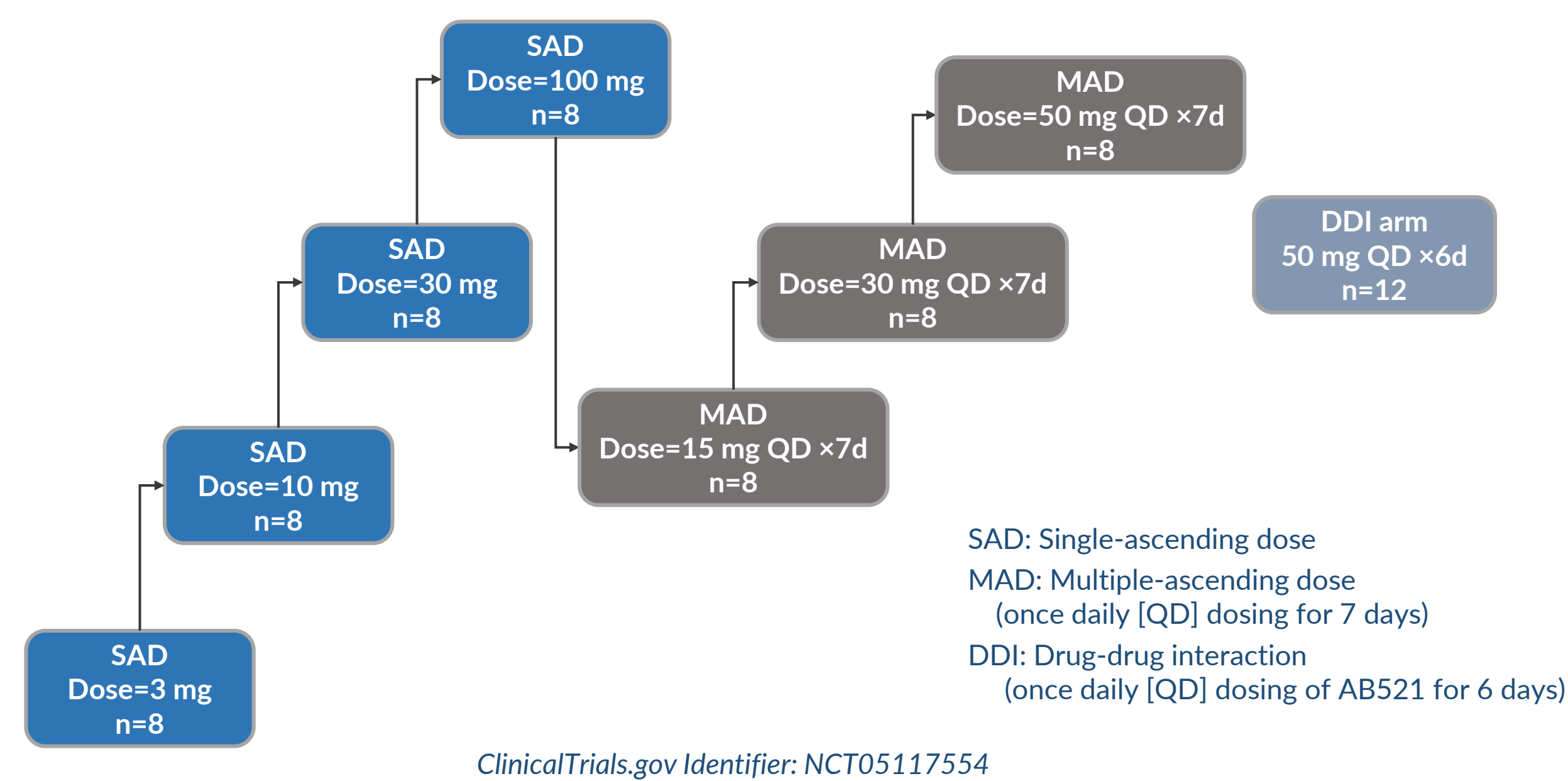
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BACKGROUND

- Hypoxia-inducible factor (HIF)-2α is a transcription factor that is an oncogenic driver in clear cell renal cell carcinoma (ccRCC)
- The post-translational regulation of the HIF-2α protein is oxygen-dependent and, in hypoxic or pseudohypoxic conditions, results in the stabilization of HIF-2α and downstream transcription of pro-tumorigenic genes
- HIF-2α inhibition has been shown clinically to mitigate tumor growth in ccRCC cases that have a high frequency of von Hippel-Lindau tumor suppressor gene mutation or dysregulation
- AB521, an orally bioavailable small-molecule inhibitor of HIF-2α, potently inhibits transcription of HIF-2α-dependent genes in cell lines and preclinical species
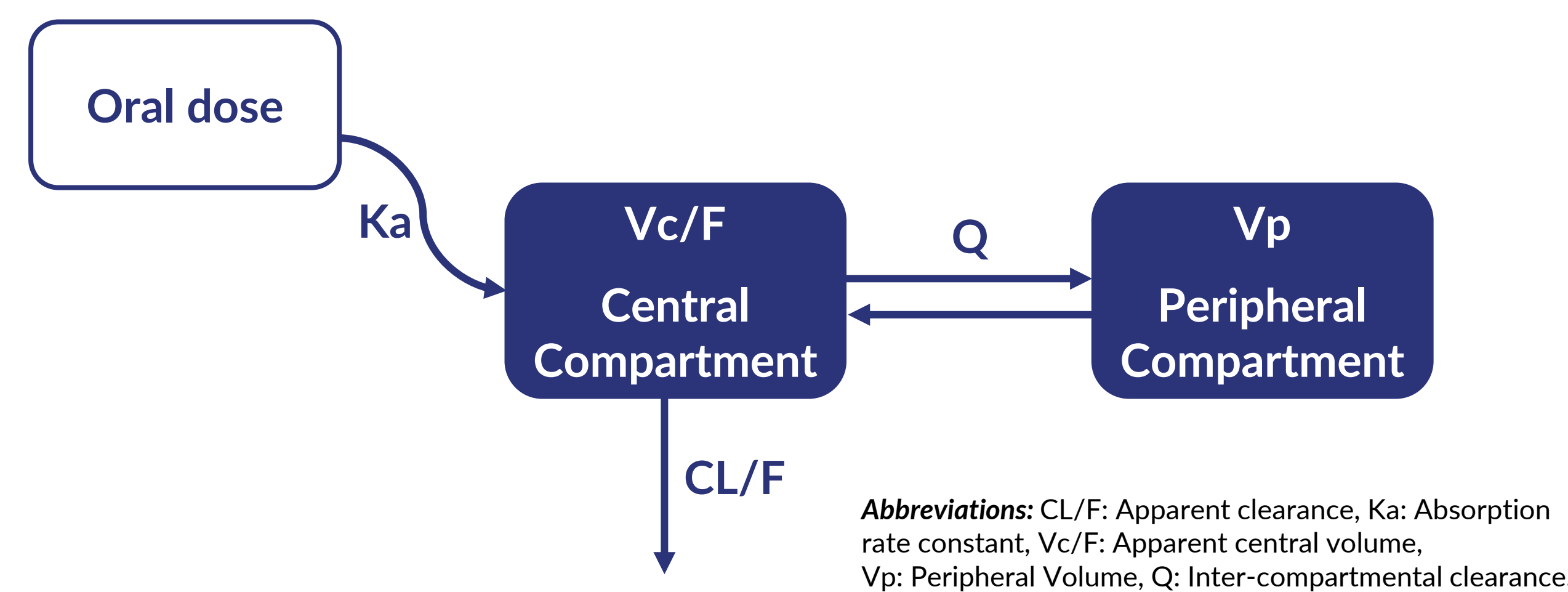
OBJECTIVES

- To develop a PopPK model describing the relationship between dose and AB521 PK
- To use model simulations to guide dose selection for future clinical trials

METHODS: CLINICAL STUDY DESIGN

- ARC-14 is a first-in-human, participant and investigator-blinded, randomized, placebo-controlled, single- and multiple-ascending dose study with drug-drug interaction, to investigate the safety, tolerability, and PK profile of AB521, in healthy volunteers
- The study enrolled a total of 70 subjects (randomized 3:1, AB521:placebo, in SAD and MAD cohorts, and active AB521 in DDI cohort)
- Final dataset for PopPK model included a total of 784 plasma observation records from 55 subjects who received AB521 (each having at least 3 post-dose data points)
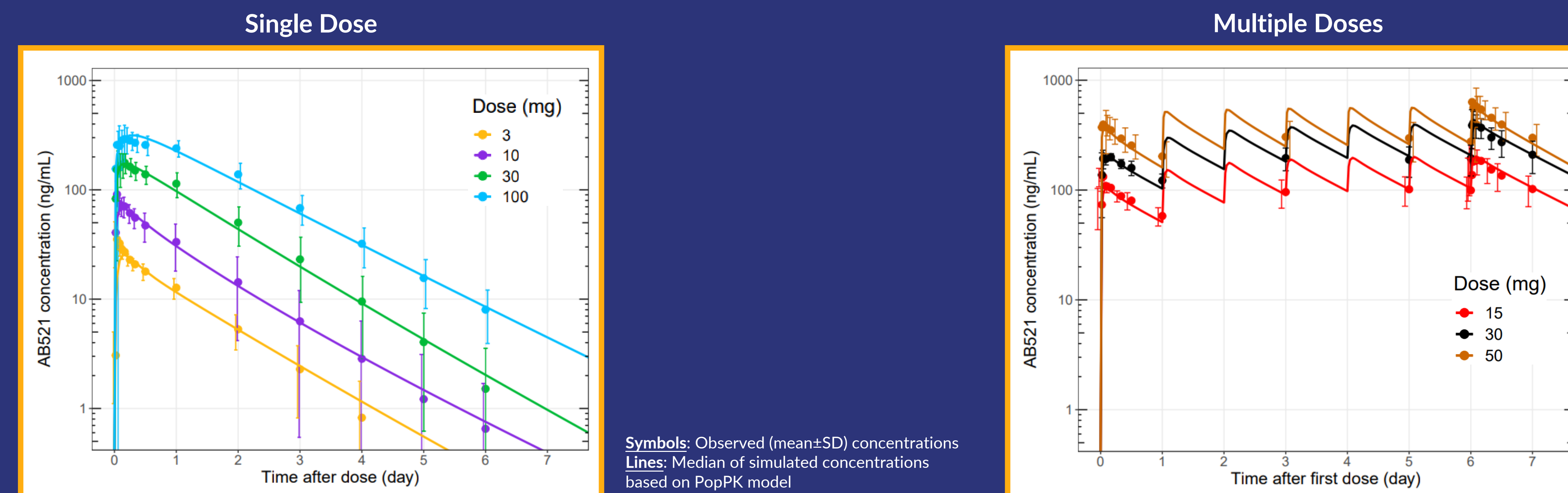

SAD: Single-ascending dose
MAD: Multiple-ascending dose (once daily [QD] dosing for 7 days)
DDI: Drug-drug interaction (once daily [QD] dosing of AB521 for 6 days)

ClinicalTrials.gov Identifier: NCT05117554

METHODS: POPULATION PK MODEL STRUCTURE

Abbreviations: CL/F: Apparent clearance, Ka: Absorption rate constant, Vc/F: Apparent central volume, Vp: Peripheral Volume, Q: Inter-compartmental clearance.
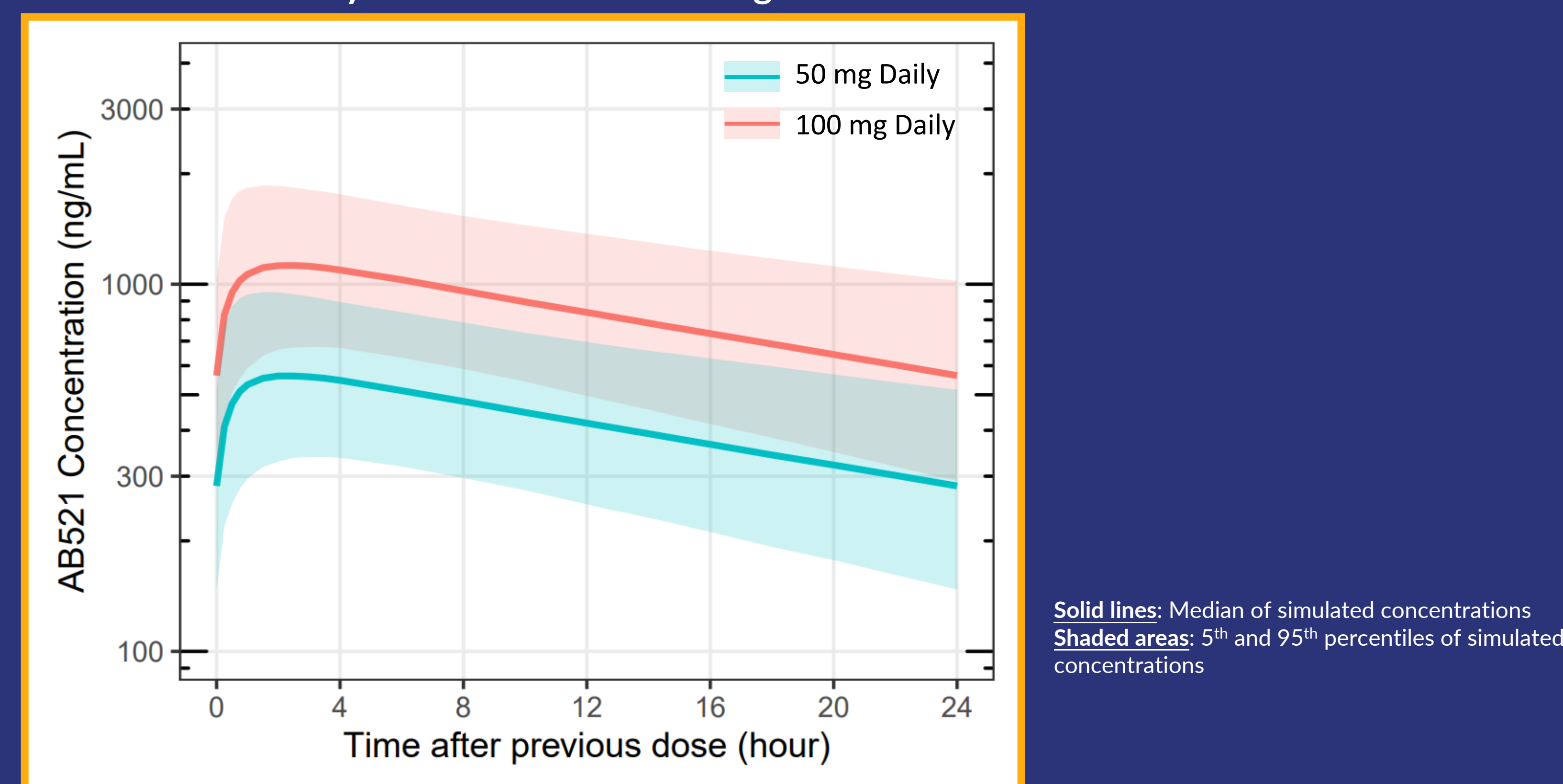
CONCLUSION

- **A preliminary PopPK model was developed to adequately describe AB521 plasma PK profile**
- **AB521 showed favorable PK profiles with:**
  - Half-life ~21 hours (estimated by PopPK) supporting once daily dosing
  - Dose-proportional increase in exposure in the dose range tested (3 mg -100 mg)
- **The model supports selection of multiple dose levels for expansion cohorts in ongoing Phase 1 study in patients, to enable exploration of the full therapeutic potential of HIF-2α inhibition**

Model adequately described the AB521 plasma PK over the dose range of 3 mg to 100 mg

Single Dose

Multiple Doses

Symbols: Observed (mean±SD) concentrations
Lines: Median of simulated concentrations based on PopPK model

Dose selection rationale based on PopPK model

- Based on simulations, 50 mg and 100 mg daily doses provide sufficiently different exposures for identifying overall trends in exposure response
- Therefore, based on these simulations and preliminary safety information, multiple dose levels, including 50 mg and 100 mg daily, were identified for expansion cohorts in the ongoing Phase 1 study in patients

PopPK Simulations of AB521 Steady-State PK Profile after Daily Doses of 50 and 100 mg

Solid lines: Median of simulated concentrations
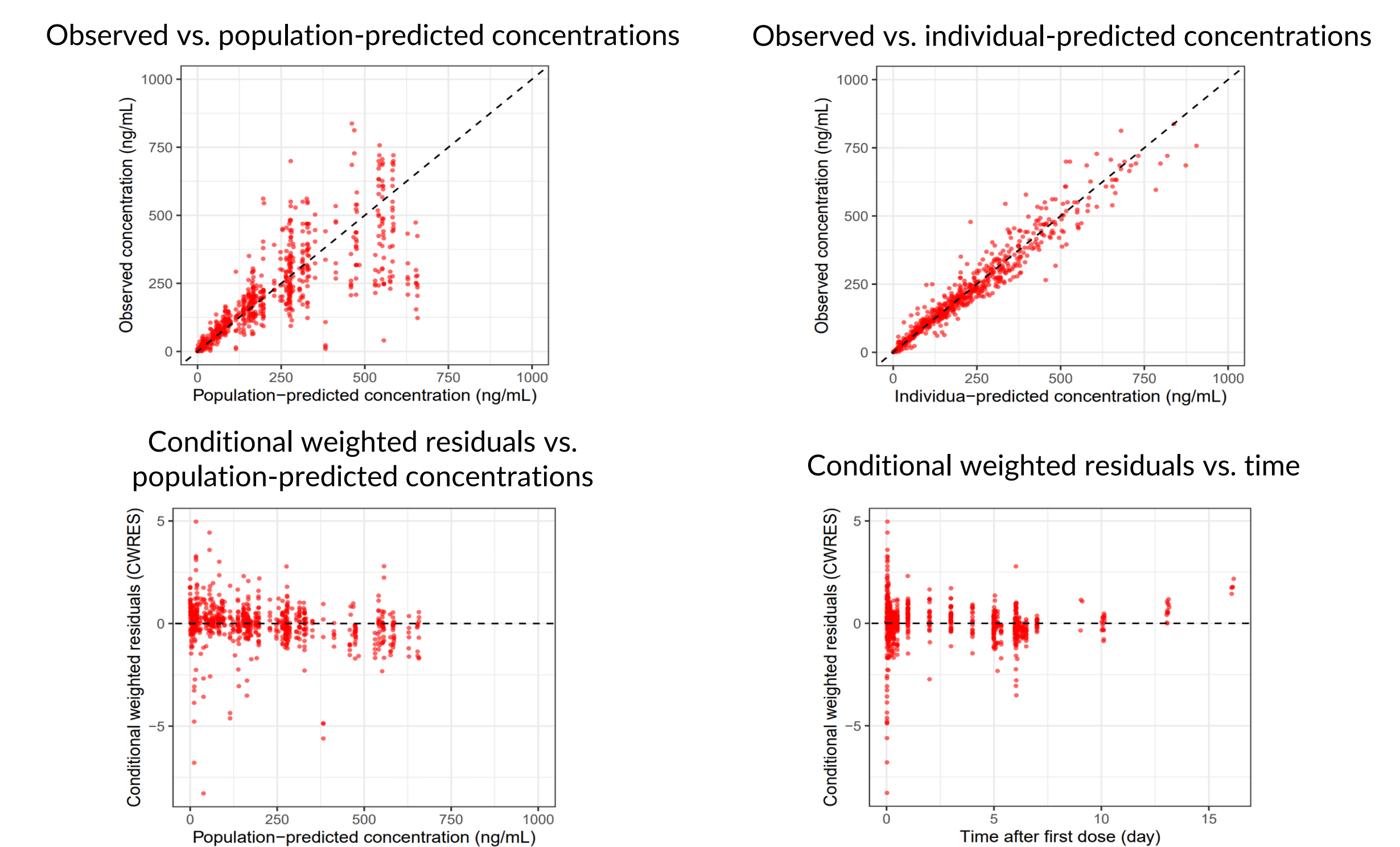**Shaded areas**: 5th and 95th percentiles of simulated concentrations

RESULTS

- A two-compartment model with first-order absorption and interindividual variability on apparent clearance, apparent central volume of distribution, peripheral volume distribution, and absorption rate constant adequately described the AB521 plasma PK across the dose range of 3 mg to 100 mg
- The half-life for AB521 estimated by PopPK modeling is ~ 21 hours supporting once daily dosing
- AB521 shows dose-proportional exposure increase in the dose range tested
- Simulations indicated that 50 mg and 100 mg daily doses provide sufficiently different exposures for identifying overall trends in exposure response
- Based on these simulations and preliminary safety information, multiple dose levels, including 50 and 100 mg daily, were identified for expansion cohorts in the ongoing Phase 1 study in patients, to enable exploration of the full therapeutic potential of HIF-2α inhibition

Parameter Estimates

Parameter	Parameter Estimate (%RSE)
Apparent clearance (CL/F) (L/h)	4.95 (4)
Apparent central volume distribution (Vc/F) (L)	132 (6)
Peripheral volume distribution (Vp) (L)	14.6 (26)
Inter-compartmental clearance (Q) (L/h)	3.82 (35)
Absorption rate constant (Ka) (1/h)	1.43 (19)
Interindividual Variability (%CV)	
$\eta_{CL/F}$	31.0 (8)
$\eta_{Vc/F}$	33.6 (12)
η_{Vp}	36.1 (30)
η_{Ka}	105 (14)
Residual Error (%CV)	
Proportional Error (additive log-transformed)	26.2 (9)

%CV: Percentage coefficient of variation; RSE: Relative standard error

Goodness-of-Fit Plots for AB521 PK

Observed vs. population-predicted concentrations

Observed vs. individual-predicted concentrations

Conditional weighted residuals vs. population-predicted concentrations

Conditional weighted residuals vs. time

METHODS: Software

- The PopPK analysis was conducted using nonlinear mixed-effects modeling with the NONMEM software, version 7.5
- Graphical and all other statistical analyses, including evaluation of NONMEM outputs, were performed using R Studio version 2023.06.1 for Windows